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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,698	08/02/2005	Andre Francois Gorenflot	I-2002.010 US	2601

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PATENT DEPARTMENT
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EXAMINER	
GANGLE, BRIAN J	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,698	GORENFLOT ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-28* is/are pending in the application.

4a) Of the above claim(s) *27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II in the response filed 8/18/2006 is acknowledged. The traversal is on the ground(s) that there is unity of invention between the inventions. This is not found persuasive for the following reasons.

Applicant argues: that the special technical feature of claim 15 is a method of making an immunogenic composition comprising a free saponin and a fusion protein, wherein the fusion protein comprises a heterologous hydrophobic polypeptide combined to the N-terminus and/or the C-terminus of a core polypeptide having at least one protective epitope. Applicant argues that the art supplied by the examiner in the restriction requirement does not anticipate this feature because the hydrophobic protein disclosed by Gozar *et al.* does not meet the requirements of having hydrophobic data points for at least 60% of its amino acids.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant is correct that the hydrophobic peptide of Gozar does not anticipate the instant invention. However, the claimed inventions still do not possess unity of invention for the following reasons. First, applicant indicates that the special technical feature of claim 15 is a method of making an immunogenic composition. If this is true, then the method of claim 15 does not possess unity with the compositions of claims 27-28, because claims 27-28 are not drawn to a method of making and therefore do not share the special technical feature (as defined by applicant) of claim 15. However, it is the examiner's position that the special technical feature which links the method of claim 15 and the compositions of claims 27-28 is an immunogenic composition comprising a free saponin and a fusion protein, wherein the fusion protein comprises a heterologous hydrophobic polypeptide combined to the N-terminus and/or the C-terminus of a core polypeptide having at least one protective epitope. As discussed in the 35 USC 102 rejections set forth below, this feature is anticipated by Chandrashekar *et al.* (US Patent 5,854,051, 1998). Therefore, the claims do not possess unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 15-28 are pending. Claims 27-28 are withdrawn as being drawn to nonelected inventions. Claims 15-26 are currently under examination.

Sequence Requirements

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § § 1.821-1.825 for the reason(s) set forth below. Full compliance with the sequence rules is required in response to this office action. See for example Table 1 and Table 2. It should be noted that the cited occurrences of improper use are only exemplary and applicant should review the specification and drawings to correct any other lack of compliance with the sequence rules.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 8. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

It should be noted that the cited occurrences of improper use are only exemplary and applicant should review the specification to correct any other use of embedded hyperlinks.

The use of the trademarks Span and Tween on page 15, and Triton and HiTrap on page 23, has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

It should be noted that the cited occurrences of improper use are only exemplary and applicant should review the specification to correct any other use of trademarks.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Information Disclosure Statement

The information disclosure statement filed 1/7/2005 has been considered. A initialed copy is enclosed.

Claim Objections

Claims 15-26 are objected to because of the following informalities: the claims are drawn, in part, to nonelected subject matter. Appropriate correction is required.

Claim 18 is objected to because of the following informalities: the claim contains genus names, which should be italicized. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims, in general, are drawn to fusion proteins containing protective epitopes against an unnamed pathogen. Dependent claims 16 and 17 are drawn specifically to fusion proteins containing protective epitopes against organisms in the phylum Apicomplexa, the class Piroplasmida, and the genus *Babesia*.

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that applicant has possession the claimed invention. To adequately describe the genus of fusion proteins containing protective epitopes, applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit a protective immune response against a given pathogen. The specification discloses Bd37 as an antigen of *Babesia divergens*, but does not disclose any other fusion proteins containing protective epitopes that are capable of eliciting a protective immune response against any other pathogen. Applicant appears to be relying on a non-patent literature journal article to provide support for the sequence of Bd37. This sequence is deemed to be essential material and according to 37 CFR 1.57, "essential material " may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. The specification further does not disclose distinguishing and identifying features of a representative number of members of the genus of fusion proteins to which the claims are drawn, such as a correlation between the structure of the immunoepitope and its recited function (i.e. eliciting protective immunity against a given pathogen), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of fusion proteins. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of fusion proteins containing protective epitopes.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan *et al.* (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of fusion proteins containing protective epitopes. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus of fusion proteins to which the claim refers.

Claims 15-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of

guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to methods of preparing an immunogenic composition comprising i) combining a heterologous hydrophobic polypeptide to the N-terminus and/or the C-terminus of a core polypeptide thereby forming a fusion protein; and

ii) mixing said fusion protein with a saponin adjuvant in a free form, thereby forming said immunogenic composition; wherein said heterologous hydrophobic polypeptide has a hydrophobicity of 0.6 or more as determined by dividing (a) by (b), wherein (a) is the number of hydrophobic data points of said heterologous hydrophobic polypeptide as determined using the Kyte-Doolittle hydrophobicity analysis using a window of 5 amino acids, and (b) is the total number of amino acids of said heterologous hydrophobic polypeptide; and wherein said core polypeptide has a protective epitope. Therefore, the claims are drawn to vaccines comprising said fusion protein.

Breadth of the claims: Claims 15 and 19-26 encompass all core polypeptides with protective epitopes against any pathogen or disease, while dependent claims 16-18 are limited to vaccines against organisms in the phylum Apicomplexa (claim 16), the class Piroplasmida (claim 17), and the genus *Babesia* (claim 18). Further, the claims encompass all heterologous hydrophobic polypeptides that have a hydrophobicity of 0.6 or more using the Kyte-Doolittle hydrophobicity analysis.

Guidance of the specification/The existence of working examples: The specification states that the hydropathy algorithm of Kyte and Doolittle is used. The specification further states, on pages 6-7, that several computer algorithms have been developed to determine

hydrophobicity and that there are differences between these programs (page 9). The specification also states that a window of 5 amino acids must be used but does not provide any further information regarding the other parameters that may affect the Kyte-Doolittle analysis. Applicant appears to be relying on a non-patent literature journal article to provide support for the algorithm needed to perform the Kyte-Doolittle analysis since they do not actually provide said algorithm. This algorithm is deemed to be essential material, and according to 37 CFR 1.57, "essential material " may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference.

The specification lists several examples of "hydrophobic peptides" for use in the instant invention (Table 1). These include melittin, DAF, CWP 1, MV HN and HHV-4 EBNA-3C. The fusion protein Bd37-DAF is shown to have protective efficacy against *Babesia divergens* Munich in a challenge experiment in gerbils. However, the specification does not provide enough information to determine if DAF, or any other protein, meets the hydrophobicity limitations of the claims. As discussed below, using certain parameters, DAF does not have a hydrophobicity of 0.6 or more, as required by the claims. No other core polypeptide with a protective epitope is disclosed and no other fusion protein containing a hydrophobic peptide was disclosed.

State of the art: While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie *et al.* further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where

such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan *et al.* (*Nature Biotechnology* **7**: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a particular immune response to a given pathogen can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of antibodies to a particular epitope, the specification, as filed, does not provide enablement for the full scope of the claims.

Furthermore, the specification does not provide the information necessary to detemine the hydrophobicity of a peptide according to the Kyte-Doolittle analysis. The specification refers to programs available to determine hydrophobicity. These programs have parameters which affect the determination of hydrophobicity. Applicant has specified a window of 5 amino acids; however, there are additional parameters that must be set, such as the weight variation model, the relative weight of the window edges, and normalization. Using the ProtScale tool at http://ca.expasy.org/tools/protscale.html, the examiner found that the peptide DAF (used by applicant as a hydrophobic peptide) had a hydrophobicity that ranged from .4 to 1, depending on the parameter settings. Additionally, ProtScale requires a peptide with a minimum length of 20 amino acids, whereas the claims have no such limitation, and the instant specification refers to peptides with as few as 3 amino acids. Moreover, the specification and claim state that the percentage hydrophobicity is determined by dividing the number of hydrophobic data points by the total number of amino acids of the heterologous hydrophobic polypeptide. The specification also refers to percentage as the percentage of data points that are hydrophobic. However, it is

noted that, at least in ProtScale, the total number of data points does not equal the total number of amino acids. Therefore, the percentage of hydrophobic data points (which would be calculated by dividing the number of hydrophobic data points by the total number of data points) is not equal to the number of hydrophobic data points divided by the total number of amino acids. In the case of DAF, this discrepancy in calculation leads to a difference of almost 10%.

Therefore, in view of the lack of support in the art and specification for protective epitopes against any given pathogen and the inability of the skilled artisan to determine whether a hydrophobic peptide meets the limitations of the claims, it would require undue experimentation on the part of the skilled artisan to make and use the vaccine as claimed; therefore the claims are not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is rendered vague and indefinite by the phrase "combining a heterologous hydrophobic polypeptide to the N-terminus and/or the C-terminus of a core polypeptide." First, it is not clear what is meant by combining a protein "to" a protein. Generally, one combines things *with* each other, not *to* each other. Further, the claim refers to combining a single protein to both the N and C-terminus of a core polypeptide. Are applicants referring to a cyclic protein, or should the term "and/or" be replaced with the term "or"?

Claim 15 is rendered vague and indefinite by the use of the term "hydrophobic polypeptide." The specification provides a definition of a hydrophobic peptide, but not of a hydrophobic polypeptide. Therefore, it is not clear whether the hydrophobic polypeptide of the claim is a full-length protein, or merely any portion of such a protein which is a hydrophobic region. If the claim refers to a portion of a protein, can the fusion protein of the claim comprise more than just this hydrophobic portion and the core polypeptide? Moreover, the claim requires

the use of the Kyte-Doolittle hydrophobicity analysis to determine hydrophobicity. What is the algorithm used to determine hydrophobicity? On pages 6-7 of the specification, applicant states that several computer algorithms have been developed to determine hydrophobicity. Applicant also states, on page 9, that there are differences between these programs. Which of these programs should be used to determine whether a peptide meets the limitations of the claims? These programs also have parameters which affect the determination of hydrophobicity. Applicant has specified a window of 5 amino acids. However, using the ProtScale tool at http://ca.expasy.org/tools/protscale.html, the examiner found that the peptide DAF (used by applicant as a hydrophobic peptide) had a hydrophobicity that ranged from .4 to 1, depending on the parameter settings. Additionally, ProtScale requires a peptide with a minimum length of 20 amino acids, whereas the claims have no such limitation, and the instant specification refers to peptides with as few as 3 amino acids. Moreover, the specification and claim state that the percentage hydrophobicity is determined by dividing the number of hydrophobic data points by the total number of amino acids of the heterologous hydrophobic polypeptide. The specification also refers to percentage as the percentage of data points that are hydrophobic. However, it is noted that, at least in ProtScale, the total number of data points does not equal the total number of amino acids. Therefore, the percentage of hydrophobic data points (which would be calculated by dividing the number of hydrophobic data points by the total number of data points) is not equal to the number of hydrophobic data points divided by the total number of amino acids. In the case of DAF, this discrepancy in calculation leads to a difference of almost 10%. Thus, it is not clear what is meant by the term "hydrophobic polypeptide" and it is not clear how one could determine whether a given peptide meets the limitations of the claim.

Claim 19 is rendered vague and indefinite by the phrase "wherein the heterologous hydrophobic peptide is from an N-terminal hydrophobic sequence." It is not clear what would constitute a peptide that is "from" an N-terminal sequence. Is this the N-terminal sequence or not? How close must a peptide be to the N-terminus to be "from" the N-terminus. What are the boundaries of an N-terminal sequence?

Claim 20 is rendered vague and indefinite by the phrase "wherein the heterologous hydrophobic peptide is from an internal hydrophobic sequence." It is not clear what would constitute a peptide that is "from" an internal hydrophobic sequence. What are the boundaries of

an "internal sequence"? Does this include peptides that are one amino acid away from the N or C-terminus?

Claim 21 is rendered vague and indefinite by the phrase "wherein the heterologous hydrophobic peptide is from an C-terminal hydrophobic sequence." It is not clear what would constitute a peptide that is "from" an C-terminal sequence. Is this the C-terminal sequence or not? How close must a peptide be to the C-terminus to be "from" the C-terminus. What are the boundaries of an C-terminal sequence?

Claims 19-21 recite the limitation "hydrophobic peptide." There is insufficient antecedent basis for this limitation in the claim. The parent claim refers to hydrophobic polypeptides.

Claims 24-26 are rendered vague and indefinite by the phrase "preparing a vaccine." What is the vaccine intended to protect against?

Claim 25 is rendered vague and indefinite by the phrase "wherein at least one additional immunoactive component is combined with said vaccine." It is not clear whether this is an active method step and when this step should occur.

Claim 26 is rendered vague and indefinite by the phrase "wherein said vaccine is freeze-dried." It is not clear whether this is an active method step and when this step should occur.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 15-19, 23-25 rejected under 35 U.S.C. 102(b) as being anticipated by Chandrashekar *et al.* (US Patent 5,854,051, 1998).

The instant claims are drawn to methods of preparing an immunogenic composition comprising i) combining a heterologous hydrophobic polypeptide to the N-terminus and/or the C-terminus of a core polypeptide thereby forming a fusion protein; and

ii) mixing said fusion protein with a saponin adjuvant in a free form, thereby forming said immunogenic composition; wherein said heterologous hydrophobic polypeptide has a hydrophobicity of 0.6 or more as determined by dividing (a) by (b), wherein (a) is the number of hydrophobic data points of said heterologous hydrophobic polypeptide as determined using the Kyte-Doolittle hydrophobicity analysis using a window of 5 amino acids, and (b) is the total number of amino acids of said heterologous hydrophobic polypeptide; and wherein said core polypeptide has a protective epitope (claim 15); wherein the core polypeptide is a component of a protein of an organism of the phylum Apicomplexa (claim 16), specifically, the class Piroplasmida (claim 17), more specifically, the genus *Babesia* (claim 18). Further limitations include where the heterologous hydrophobic peptide is from an N-terminal hydrophobic sequence (claim 19), where the saponin is Quillaja saponin (claim 23); where the immunogenic composition is a vaccine and is mixed with a pharmaceutically acceptable carrier (claim 24); and where at least one additional immunoactive component is combined with said vaccine (claim 25).

Chandrashekar *et al.* disclose a method of making an immunogenic composition wherein a fusion protein is mixed with a QuilA saponin (column 20, lines 28-32 and line 53). The fusion protein comprises, as a core polypeptide containing a protective epitope, a parasitic helminth asparaginase protein-containing domain and an additional protein from the genus *Babesia* (column 9, lines 1-4 and 35-50; and column 10, line 15). The fusion protein also contains, as a hydrophobic polypeptide, tissue plasminogen activator, which is disclosed in the instant specification as an N-terminal hydrophobic polypeptide (page 7, lines 25-35). The disclosed vaccine also contains additional immunoactive agents and a pharmaceutically acceptable carrier (column 19, lines 49-55 and column 20, lines 7-27). It should be noted that, taxologically, the genus *Babesia* falls within the class Piroplasmida, which falls within the phylum Apicomplexa.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brian Gangle
AU 1645

ROBERT A. ZEMAN
PRIMARY EXAMINER